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Distinguishing Features of Ocular Sarcoidosis in an International Cohort of Uveitis Patients

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Purpose: To determine which clinical features distinguish ocular sarcoidosis from other forms of uveitis in an international population and to estimate the sensitivity and specificity of the International Workshop on Ocular Sarcoidosis (IWOS) clinical signs and laboratory tests.

Design: Multicenter, retrospective medical record review.

Participants: Eight hundred eighty-four patients with uveitis from 19 centers in 12 countries.

Methods: Data collected included suspected cause of uveitis, clinical findings, and laboratory investigations within 6 months of presentation. The IWOS criteria were used to classify patients as having definite (biopsy-proven), presumed (evidence of bilateral hilar lymphadenopathy [BHL] on chest radiograph or CT scan), probable, or possible ocular sarcoidosis. Patients with biopsy positive results or BHL on chest radiograph or CT scan were considered sarcoidosis cases.

Main Outcome Measures: Sensitivity and specificity of clinical signs and laboratory investigations for diagnosing ocular sarcoidosis.

Results: Of the 884 uveitis patients, 264 (30%) were suspected to have ocular sarcoidosis. One hundred eighty patients (20%) met the IWOS criteria; 98 were definite (biopsy-proven) disease, 69 presumed disease (BHL), 10 probable disease, and 3 possible disease. Among sarcoidosis cases, the most common clinical signs were bilaterality (86%); snowballs or string of pearls (50%); mutton-fat keratic precipitates, iris nodules, or both (46%); and multiple chorioretinal peripheral lesions (45%). Sixty-two percent of sarcoidosis cases had elevated angiotensin converting enzyme or lysozyme and 5% demonstrated abnormal liver enzyme test results. Of the patients suspected of having sarcoidosis, 97 (37%) did not meet the IWOS criteria.

Conclusions: With the exception of BHL, IWOS clinical findings and investigational tests had low sensitivities for diagnosing ocular sarcoidosis. In particular, liver function tests seem to have little usefulness in diagnosing ocular sarcoidosis. Many patients suspected of having sarcoidosis did not fit into the classification system, indicating that the guidelines may need to be reconsidered. Adding novel laboratory tests and using more advanced statistical methods may lead to the development of a more generalizable classification system. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

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Sarcoidosis is a chronic inflammatory disease of unknown cause that is multisystemic, affecting major organs such as the lungs, lymph nodes, eyes, skin, and liver. Approximately 30% to 60% of patients with sarcoidosis demonstrate ocular involvement, often in the form of bilateral, granulomatous intraocular inflammation.[1–10] The proportion of patients who show ocular involvement may differ according to the patient population under study; for example, 50% to 94% of patients with sarcoidosis in Japan demonstrate ocular symptoms, and there is evidence that black patients are more likely to demonstrate ocular symptoms than white patients.[7,11–13]

Uveitis is inflammation in the eye that encompasses a number of disease entities. Sarcoidosis is one of the major diseases associated with uveitis and is the leading cause of uveitis in Japan.[14] Uveitis resulting from sarcoidosis often is referred to as ocular sarcoidosis. Ocular sarcoidosis is not a separate disease from sarcoidosis, but is used to refer to sarcoidosis patients who exhibit ocular symptoms with or without systemic manifestations.

Diagnosing sarcoidosis remains extremely difficult. The gold standard for making a definitive diagnosis involves a biopsy of relevant tissue. In many cases, it is the manifestation of ocular symptoms that leads to the detection of sarcoidosis.[6,7,15] However, biopsies of intraocular tissue generally are not performed because they are invasive and can result in loss of vision. There has not been sufficient evidence to support the usefulness of conjunctival and lacrimal gland biopsies for diagnosing ocular sarcoidosis, particularly for uveitis patients.[16] Biopsies of the lung, skin, or lymph nodes also may generate a definitive diagnosis, but these procedures are not always acceptable to patients.

Effort has been made to determine which clinical signs and laboratory results are useful in correctly diagnosing sarcoidosis in patients with uveitis. In 2009, the International Workshop on Ocular Sarcoidosis (IWOS) drafted a

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set of guidelines for characterizing uveitis patients suspected of having sarcoidosis. These guidelines designate 4 diagnostic categories for uveitis: definite, presumed, probable, or possible ocular sarcoidosis (Tables 1A,B).[17] There has been one study to validate the IWOS diagnostic criteria in a Japanese population,[18] but the criteria's generalizability to the international population is unclear.

The purpose of this study was to determine which clinical features distinguish ocular sarcoidosis from other forms of uveitis in an international population. We described the clinical characteristics and laboratory findings of patients with biopsy-proven sarcoidosis, compared the clinical features of uveitis patients with and without a suspected diagnosis of sarcoidosis, and estimated the sensitivity and specificity of IWOS clinical signs and laboratory tests.

Methods

Data were collected from 19 uveitis clinics in 12 countries. Institutional review board or ethics committee approval was obtained at the University of California, San Francisco, and at each study site. The study complied with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. The study clinics were located at: Tokyo Medical and Dental University Hospital (Japan), Kyorin University School of Medicine (Japan), National Defense Medical College (Japan), Narayana Nethralaya (India), Sankara Nethralaya (India), Prabha Eye Clinic (India), Asociación Para Evitar la Ceguera en México (Mexico), Peking Union Medical College Hospital (China), Kaohsiung Veterans General Hospital (Taiwan), University Hospital of Padova (Italy), Université libre de Bruxelles (Belgium), Bellvitge University Hospital (Spain), University of Tübingen (Germany), Fattouma Bourguiba University Hospital (Tunisia), The World Eye Center (Turkey), the Cole Eye Institute of Cleveland Clinic (United States), the University of Illinois at Chicago (United States), the Francis I. Proctor Foundation at the University of California, San Francisco (United States), and the Roski Eye Institute of the University of Southern California (United States).

Table 1A. Clinical Signs and Laboratory Investigations Considered to Be Suggestive of Ocular Sarcoidosis by the International Workshop on Ocular Sarcoidosis 2009[17]

IWOS clinical signs suggestive of ocular sarcoidosis
1. Mutton-fat keratic precipitates (large and small), iris nodules at pupillary margin (Koeppe) or in stroma (Busacca), or both
2. Trabecular meshwork nodules, tent-shaped peripheral anterior synechiae, or both
3. Snowball or string-of-pearls vitreous opacities
4. Multiple chorioretinal peripheral lesions (active and atrophic)
5. Nodular or segmental periphlebitis, macroaneurysm, or both
6. Optic disc nodule(s) or granuloma(s), solitary choroidal nodule, or both
7. Bilaterality
IWOS laboratory investigations in suspected ocular sarcoidosis
1. Negative tuberculin test results in a BCG-vaccinated patient or having shown positive PPD (or Mantoux) skin test results previously
2. Elevated serum ACE or serum lysozyme levels, or both
3. Chest radiography to examine for BHL
4. Abnormal liver enzyme test results (alkaline phosphatase >3 times the upper limit of normal or any 2 of alkaline phosphatase, AST, ALT, LDH, or GGT >2 times the upper limit of normal)
5. BHL on chest CT scan in patients with negative chest x-ray

ACE = angiotensin converting enzyme; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCG = bacillus Calmette–Guérin; BHL = bilateral hilar lymphadenopathy; CT = computed tomography; GGT = γ-glutamyl transferase; IWOS = International Workshop on Ocular Sarcoidosis; LDH = lactate dehydrogenase; PPD = purified protein derivative.

Table 1B. Diagnostic Criteria for Ocular Sarcoidosis Developed by the International Workshop on Ocular Sarcoidosis 2009[17]

All other possible causes of uveitis, in particular tuberculous uveitis, have to be ruled out	
Definite	Biopsy-supported diagnosis with a compatible uveitis
Presumed	Biopsy not performed, presence of BHL with a compatible uveitis
Probable	Biopsy not performed, BHL negative, with 3 clinical signs and 2 positive laboratory test results
Possible	Biopsy results negative, 4 clinical signs, and 2 positive laboratory test results

All patients with uveitis and 6 months or more of follow-up were eligible for the study. Clinics were asked to submit up to 100 consecutive uveitis cases identified through recent retrospective chart review. However, a sufficient number of patients who underwent a biopsy were needed to address the study aims, and therefore, clinics were asked specifically to include patients who had undergone a recent biopsy. Data collection occurred between January 2011 and April 2015. A standard data collection form was distributed to all sites, and study data were collected and managed using Research Electronic Data Capture hosted at University of California, San Francisco.[19] At presentation, clinical findings, patient demographics, suspected cause of uveitis, and anatomic location were recorded. Clinical findings at presentation were based on the IWOS clinical intraocular signs and included: laterality; keratic precipitates (KPs); iris nodules at the pupillary margin or in stroma; trabecular meshwork nodules; tent-shaped peripheral anterior synechiae; snowball or string-of-pearls vitreous opacities; multiple chorioretinal peripheral lesions (active, atrophic, or both); nodular or segmental retinal periphlebitis (with or without candlewax drippings); macroaneurysm in an inflamed eye; optic disc nodules or granulomas; and solitary choroidal nodule. Clinical intraocular signs were counted if present in at least one eye. We also collected the results from the diagnostic workup and the suspected cause of uveitis at 6 months. The following laboratory investigation results were collected: tuberculin purified protein derivative skin test, interferon-gamma release assay, syphilis testing, serum angiotensin converting enzyme (ACE), serum lysozyme, liver enzyme tests (alkaline phosphatase, aspartate transaminase, alanine transaminase, lactate dehydrogenase, γ-glutamyl transferase), chest radiograph, chest computed tomography (CT) scan, and biopsy if performed. It was not known if a patient had received a bacille Calmette-Guerin (BCG) vaccine; therefore, patients from countries where BCG vaccinations commonly are administered were assumed to be vaccinated. In addition, the suspected diagnosis of uveitis was collected at the 12-month follow-up.

The IWOS clinical intraocular signs and laboratory investigation criteria are listed in Table 1A and were used to classify patients as having definite, presumed, probable, or possible ocular sarcoidosis (Table 1B). Patients who did not meet the IWOS ocular sarcoidosis criteria were categorized as having infectious, noninfectious, tuberculosis-associated, or idiopathic uveitis based on the clinician's diagnosis. Patients who did not meet 1 of the IWOS categories, but for whom the clinician suspected sarcoidosis, were categorized as having clinician-suspected sarcoidosis. The frequency of the IWOS clinical signs were